BAD BLOOD: PLACENTAL EVOLUTION, PARENT-OFFSPRING CONFLICT, AND OBSTETRIC DISORDERS

By

ERIKA JEAN ALBRECHT

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A Thesis Submitted to The Honors College

In Partial Fulfillment of the Bachelors degree
With Honors in

Anthropology (Human Biology emphasis)

THE UNIVERSITY OF ARIZONA

D E C E M B E R 2 0 1 9

Approved by:

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Dr. Ivy Pike
Department of Anthropology

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Abstract

This thesis, in the form of a literature review, surveys the body of knowledge pertaining to the human placenta. It begins with an introduction to placental morphology and human placental evolution in a comparative anatomy context, demonstrating the special role of placental invasiveness in humans. Next, discussions of parent-offspring conflict, parent-of-origin imprinting, life history theory, and plasticity explore the adaptive value of human placental morphology and function. The thesis concludes with an overview of obstetric disorders and their relationship to the trajectory of human placental evolution. I emphasize the importance of the parent-offspring conflict in understanding the evolution of human placental physiology and variation, as well as resultant obstetric disorders.

Introduction

To paraphrase an axiom in the growing practice of evolutionary medicine: it is only through the lens of evolution that the biology of medicine can be truly understood. Evolutionary medicine is a framework through which evolutionary insights provide context and nuance for pathology. In an overview of evolutionary medicine, Stephen C. Stearns describes evolutionary medicine not as a field, but as a "set of concepts" (Stearns, 2012). For example, Stearns highlights the progression from W. D. Hamilton's kin selection theory to Robert Trivers' parent-offspring conflict and Tyler Moore and David Haig's contemporary research on parent-of-origin imprinting (Stearns, 2012). This particular set of concepts is of singular interest in the study of human placentation. Despite its essential role as a means of fetal development and as a predictor of adult health, the placenta is frequently overlooked as merely a by-product of gestation. Placental variation within and among eutherian mammal species predicts vital maternal health outcomes. Moreover, the placenta surpasses every other mammalian organ in terms of structural variation (Crespi & Semeniuk, 2004). Common obstetric syndromes related to placentation include intrauterine growth restriction, pre-eclampsia and post-partum hemorrhage. This paper seeks to place these obstetric syndromes in the context of human placental evolution, specifically focusing on the role of invasiveness, parent-offspring conflict, and parent-of-origin imprinting.

Placental Structure and Classification

The placenta is a major, albeit temporary, organ that develops during gestation and is expelled following childbirth. It is the primary means through which gases and nutrients are exchanged between mother and fetus (Emery Thompson, 2013). M. L. Power and J. Schulkin describe the placenta as a "central regulator of maternal and fetal physiology" (Power & Schulkin, 2005, p. 2). This description is ascribed due to the analogous production of hormones in the

placenta, such as cortisol and oxytocin, as in the brain. Therefore, in terms of regulatory function, the placenta serves as a quasi-central nervous system (Power & Schulkin, 2005). Following conception, the trophoblast cells, derived from the early embryo, implant into the maternal endometrium and begin to form the essential structure of the placenta (Emery Thompson, 2013). To describe the placenta, three useful characteristics may be applied: "placental shape, maternal-fetal interdigitation, [and] intimacy of the maternal-fetal interface" (Gundling & Wildman, 2015, p. 1).

Placental shape describes the overall shape, pattern, and surface area of the structure, which in turn mediates the amount of maternal-fetal nutrient exchange. In primates, the three placental shapes that have been identified are diffuse, discoid, and bidiscoid (Gundling & Wildman, 2015). In humans, the placental shape is discoid. Maternal-fetal interdigitation pattern refers to how the maternal and fetal bloodstreams are arranged, which "partially determines the physiological diffusion efficiency of the various molecules exchanged between mother and fetus (Lager & Powell, 2012)" (Gundling & Wildman, 2015, p.1). The five types are labyrinthine, villous, trabecular, lamellar, and folded. In the primate suborder Strepsirrhini, which includes lemurs and lorises, and Catarrhini, which includes orangutans and humans, the placenta consists of a villous interdigitation pattern. This pattern results in the fetal villi branching into the endometrium (Gundling & Wildman, 2015). It has been hypothesized that this particular type of maternal-fetal interdigitation is an expression of an evolutionary compromise, in which the length of pregnancies could increase without unsustainable energetic demand on the mother (Wildman et al., 2006).

The maternal-fetal interface is "one of the most studied characteristics that can be used to classify eutherian placentas (Benirschke & Kaufmann, 2000)" (Gundling & Wildman, 2015, p. 2). Put simply, the maternal-fetal interface describes the barrier through which the blood supplies of

the mother and the fetus are interwoven (Gundling & Wildman, 2015). The maternal-fetal interface can be classified into three types per the Grosser classification (Benirschke, 2007). These types are distinguished from one another by the number of layers between the fetal trophoblast cells and the maternal endometrial surface, or how intimately the trophoblast disturbs the maternal endometrium (Benirschke, 2007; Emery Thompson, 2013; Gundling & Wildman, 2015). The classifications can be ordered by levels of invasiveness, the least invasive type being epitheliochorial, followed by the moderate endotheliochorial type and the most invasive hemochorial type. Disturbance is minimal in epitheliochorial placentation; therefore, interaction between maternal and fetal blood supplies is limited (Emery Thompson, 2013; Gundling & Wildman, 2015). The endotheliochorial interface results in the degradation of the maternal epithelium and the adjacent placement of the trophoblast and the maternal endothelium. Finally, in the hemochorial interface, the trophoblast penetrates into the endometrium, degrading the maternal epithelial and endothelial cells, thereby 'remodeling' the maternal tissues. This allows the fetus direct access to the maternal blood supply. As the level of invasiveness increases in the hemochorial type, the tolerance of the maternal immune system must also increase in order to accommodate the paternal antigens present in the placenta (Gundling & Wildman, 2015).

It has been determined that the hemochorial type is the ancestral maternal-fetal interface type for extant placental mammals. Moreover, it is the most common interface among eutherian mammals (Gundling & Wildman, 2015). However, there are some exceptions; for example, the maternal-fetal interface of strepsirrhines is of the epitheliochorial type. From a phylogenetic standpoint, strepsirrhines, which have a relatively remote relationship to haplorrhines within the primate order, exhibit the opposite interface to haplorrhines in terms of invasiveness. Furthermore, even within haplorrhines, "hominoids undergo extremes of placenta invasion (Benirschke et al.,

2012, Carter & Pijnenborg, 2011)" (Emery Thompson, 2013). As such, a considerable amount of variation in placental invasiveness exists within and between species.

Evolutionary History and Comparative Anatomy

The placenta has its evolutionary origins in bird eggs, from which the mammalian state of the placenta evolved under intensive selective pressure (Benirschke, 2007; Wildman et al., 2006). According to Wildman et al., "the hemochorial and discoid placentas found in humans represent ancient mammalian character states that emerged well before the origin of primates" (Wildman et al., 2006, p. 3206). Therefore, previous assumptions that the eutherian placenta evolved from a state of relatively minimal invasiveness to a state of high invasiveness are inaccurate. Within the hemochorial type, variation can be noted. For example, Thompson compiled data from wild primates and human hunter-gatherers to compare such attributes as the type of maternal-fetal interface and fetal growth rate. While the yellow baboon (Papio cynocephalus), chimpanzee (Pan troglodytes), and human (Homo sapiens) are all haplorrhines with a hemochorial maternal-fetal interface, there are differences in the level of invasiveness and fetal growth rate. Namely, while the yellow baboon's placental form is noted as "moderately invasive," its chimpanzee and human counterparts are described as "highly invasive" (Emery Thompson, 2013).

The fetal growth rate is lowest in the yellow baboon at 5.3 grams per day, as contrasted with the chimpanzee fetal growth rate at 7.9 grams per day and the human fetal growth rate at 12.5 grams per day. Furthermore, humans and chimpanzees are part of the Hominidae family, whereas yellow baboons belong to the Cercopithecidae family. This implies a trend towards invasiveness and fetal growth in the Hominidae family during the divergence from other haplorrhines. It is important to note that while the fetal growth rate is higher in humans and

chimpanzees than in baboons, the fetal growth rate in primates is slower than mammals in general (Emery Thompson, 2013).

Variations across clades may be limited to certain placental characteristics; for example, both haplorrhine primates and ferungulates have the same maternal interdigitation, yet different shapes and interfaces. Changes from the ancestral eutherian mammalian placenta to the modern human placenta were minimal, the only notable difference being a change from labyrinthine to villous maternal-fetal interdigitation. As even the earliest eutherians had a deeply invasive placenta, it can be assumed that "the major role of the placenta in sustaining pregnancy and promoting gestational development existed throughout the eutherian lineage" (Wildman et al., 2006, p. 3203).

While Thompson's data show a correlation between maternal-fetal interface and fetal growth rate, this cannot be extended to placental efficiency. Placental efficiency in mammals with hemochorial placentas is reduced as compared to epitheliochorial mammals (Emery Thompson, 2013). Selective pressures on placental invasion and efficiency are complex and varying, impacted by multiple factors which may include "nutritional demand, gestational length, number of embryos per pregnancy, uterine shape, and maternal body constitution," (Wildman et al., 2006, p. 3203) or perhaps different vascular and transport systems (Emery Thompson, 2013). Therefore, there is no straightforward correlation between maternal-fetal interface and efficiency.

Adaptive Value of the Human Placenta

For many, pregnancy represents a "cooperative interaction between a mother and her fetus" (Haig, 1993, p. 495). In an online article for the magazine *Parents*, the placenta is elegantly described as "your baby's lifeline" that provides "the perfect environment for your new baby" (Schwarz, n.d.). However, this paradisiacal description is not entirely consistent with the

underlying evolutionary processes that have produced the placenta in its current form. An evolutionary conflict known as the parent-offspring conflict was crucial to the development of human placentation (Crespi & Semeniuk, 2004). In order to understand the human placenta, it is imperative that one examine the parent-offspring conflict, as well as genomic, or parent-of-origin, imprinting. Evolutionary biologist Robert Trivers made headway in the study of the parent-offspring conflict theory, which describes the evolutionary conflict between parent and offspring. This conflict is predicated upon the idea that offspring and parent have different preferences for parental investment. Trivers defines parental investment as "anything done by the parent for the offspring that increases the offspring's chance of surviving while decreasing the parent's ability to invest in other offspring" (Trivers, 1974, p. 249).

In the context of pregnancy, the allocation of maternal investment is particularly contentious. The parent-offspring conflict in this setting can be more aptly specified as the maternal-fetal conflict. The maternal-fetal conflict, in which fetus and mother contend for control of the maternal nutrient supply, represents one of the major adaptive changes in the evolution of the human placenta (Roberts, Green, & Schulz, 2016). In terms of reproductive success, it is ideal that the mother distribute nutritional investment equally among her offspring across her reproductive lifespan. Meanwhile, an individual offspring seeks more parental investment from the mother than would be allocated in an egalitarian manner. This 'selfish' behavior on the part of an individual offspring is due to the fact that said individual is "more closely related to itself…than it is to any given full sibling" (Crespi & Semeniuk, 2004). In order to maximize the amount of its own genetic material being passed on to future generations, an individual offspring will prioritize its own reproductive success over that of a sibling, who is not genetically identical, by extracting as much from the mother as possible (Gundling & Wildman, 2015; Haig, 1993). As the current

offspring maximizes maternal investment through deeper trophoblastic investment, “the survivability of future offspring is affected…limiting the amount of resources available to the offspring's future siblings (Trivers, 1974)” (Gundling & Wildman, 2015, p. 6).

Per Crespi and Semeniuk, four sources of genes mediate the parent-offspring conflict: “genes expressed in the mother, maternally derived genes expressed in the offspring, paternally derived genes expressed in the offspring, and genes expressed in the offspring regardless of their parental source (Trivers, 1974; Haig & Westoby, 1989; Haig & Trivers, 1995; Haig, 1997; Haig, 1999; Haig, 2000; Ubeda & Haig 2003)” (Crespi & Semeniuk, 2004, p. 636). The role of these genes can be explained in terms of genomic imprinting, a phenomenon similar to the paternal-offspring conflict. Genomic imprinting is the manner in which an allele can be either maternally or paternally expressed for a trait, resulting in an evolutionary arms race. During pregnancy, the expression of either the maternally derived or the paternally derived gene can determine the extent of maternal investment. Namely, paternally derived genes promote fetal growth, thereby increasing the demand for resources on the mother, while maternally derived genes suppress fetal growth. This trend matches the evolutionary interests of the father. As the father cannot assume that the mother’s future offspring will be his, it is in the father’s best interest to promote the success of the current offspring. In general, “either the maternally derived or paternally derived allele [is] transcriptionally silenced,” while the other is expressed, in the form of monoallelic expression (Wilkins, 2011, p. 538). The evolutionary explanation for this phenomenon is referred to as the Kinship Theory of Imprinting, which states that the “inclusive fitness of a maternally derived allele is not identical to that of a paternally derived allele (Haig 2000; Wilkins & Haig 2003)” (Wilkins, 2011, p. 538).

Parent-of-origin imprinting provides important nuance to human life-history theory. For example, intense suckling during nursing is associated with paternally derived genes. Evidently, the infant is able to secure more nutrients from the mother than may match the mother's optimum parental investment. Specifically relating life-history theory with gestation, Haig claims that "longer gestation in humans enhanced the average fitness of offspring but reduced the average fitness of their mothers" (Haig, 2010). Important characteristics of human life history include early weaning and slow maturation. In terms of the parent-offspring conflict, slow maturation in children allows the child greater access to maternal resources in lieu of that access being divided amongst her other offspring. Although this reduces maternal fitness, this reduction is combatted by the mother in the form of early weaning, which shortens the interbirth interval, thereby increasing maternal reproductive success (Haig, 2010).

In addition to the struggle for the maternal blood supply, another adaptive change that contributed to the evolution of the human placenta, closely related to parent-of-origin imprinting, was the avoidance of immune rejection. According to Roberts, Green, and Schulz, in order to "minimize attention from various arms of the maternal immune system, the trophoblast must continue to evolve counter-measures for its own protection and even advantage" (Roberts, Green, & Schulz, 2016, p. 185). One example of fetal manipulation of the maternal immune system are cadherins—cell surface adhesion proteins that play a role in mediating maternal-fetal interactions during implantation and placentation (Summers & Crespi, 2005). Among their functions, cadherins regulate inter-cellular recognition and maternal-fetal resource transport. How successfully cadherins from both sides of the maternal-fetal interface bind can determine the amount of resources transferred (Summers & Crespi, 2005).

The success of their role is explained by Haig through the concept of "green-beard" genes. Green-beards are genes that can recognize themselves in other individuals and cause that individual to support the form of the gene that is featured in the individual. There are two features of cadherins that make them ideal green-beards. The first is that "they have modular extracellular domains that recognize and specifically bind copies of themselves on other cells (Haig, 1996)"; the second is that "they have cytoplasmic domains that allow them to influence cellular behavior (Haig, 1996)" (Summers & Crespi, 2005, p. 644). In order for cadherins to be accurately identified as green-beards, fetal cadherins must recognize maternal cadherins and prompt the maternal side to promote cadherin function. According to Haig, "genetic self-recognition at the maternal-fetal interface would enable genes for green-beards in maternal NK cells [natural killer cells of the immune system] to give green-bearded embryos greater access to maternal resources in preference to their clean-shaven sibs" (Haig, 1996, p. 6548).

There are multiple other mechanisms through which fetuses manipulate the level of maternal investment. These mechanisms pertain to the release of hormones, steroids, cytokines, and growth factors into the maternal bloodstream, as well as the manipulation of the maternal vasculature (Haig, 1993; Roberts et al., 2016). For example, these hormones "likely play a role in raising the concentrations of nutrients in maternal blood and facilitating their uptake by the placenta" (Roberts et al., 2016, p. 184). The release of these substances "signal[s] the presence of the conceptus, facilitate[s] invasion of the uterine lining, stimulate[s] angiogenesis, locally modulate[s] the mother's immune response in the uterus, maintain[s] the early stages of the pregnancy, and control[s] gestation length (Haig, 1993; Haig, 1999)" (Crespi & Semeniuk, 2004, p. 639). Examples of hormones that allow the fetus greater control over the maternal bloodstream include human chorionic gonadotropic (hCG) and human placental lactogen (hPL). The latter

increases the mother's resistance to insulin, disrupting the regulation of blood glucose levels. This can ultimately lead to gestational diabetes, "if the mother is unable to mount an adequate response to fetal manipulation" (Haig, 1993, p. 495). However, hPL is "is countered by increased maternal production of insulin" (Haig, 1993, p. 495), demonstrating how these control-seeking mechanisms escalate as each side of the conflict responds to insurgences.

In early pregnancy, the mother exerts relatively greater control over the level of parental investment. However, this changes upon implantation, in which the fetus gains the upper hand in determining nutrient allocation and timing of parturition (Haig, 2010). During this time, the fetally derived cells of the trophoblast remodel the maternal endometrium. The mother's vasculature autonomy is compromised as the arterial vessels are no longer able to constrict. As the fetus benefits from greater control over and access to the maternal blood supply, the mother "cannot reduce the nutrient content of blood reaching the placenta without reducing the nutrient supply to her own tissues" (Haig, 1993, p. 495). In the evolutionary 'tug-of-war' between mother and fetus, the placenta is a battlefield that is highly responsive to fluctuation and change.

The adaptive and responsive qualities of the placenta underlie its ability to undergo plasticity. Plasticity is the adaptability of an organism to its environment. It refers to the developmental, intergenerational changes in phenotype that occur in a shorter timeframe than that of evolutionary time. According to Kuzawa and Bragg, "the transience of many of the ecological challenges that populations confront may not be dealt with effectively by changes in gene frequencies, which require many generations and hundreds if not thousands of years to accrue in the gene pool" (Kuzawa & Bragg, 2012, p. 371). Among the environmental factors that have been linked to placental plasticity are insufficient nutrition and high altitude during gestation (Gundling & Wildman, 2015).

A highly investigated example of the latter pertains to native populations of Tibet and the Andes. At high altitudes, it becomes more difficult for vascular systems to process oxygen due to low air pressure. This is no less true in the vascular systems of the placenta, in which the abundant transfer of oxygen from mother to fetus is vital to fetal success. Maternal-fetal blood flow through the uterine artery is reduced in pregnancies at high altitudes such as Tibetan Plateau and the Andes Mountains, impairing third trimester fetal growth. (Moore et al., 2004). However, this is not the case for mothers "who have an ancestral pattern of high altitude hypoxia. These infants exhibit birth-weights comparable to those at sea-level, suggesting some level of adaptation to the hypoxic environment (Beall, 2007)" (Gundling & Wildman, 2015, p. 5). The differential health outcomes of multigenerational residents and new residents suggest adaptation to hypoxic conditions during pregnancy in the form of varying maternal vascular responses (Moore et al., 2004). Moore et al. argue that the varying maternal vascular responses have been regulated by the hypoxia-inducible factor (HIF). To support this hypothesis, Moore et al. point to the fact that a peptide which regulates vascular constriction, endothelin-1 (ET-1), targeted by HIF, falls to a normal level in long-term high-altitude residents but is higher in European women at those altitudes (Moore et al., 2004). Lower vascular constriction would allow for greater exchange of oxygen through the blood, thus resolving the risk of low oxygen transfer across the placenta. Other placental differences to promote oxygen exchange for long-term high-altitude residents are "increased capillary surface area and greater placental mass (Mathieu-Costello, 2001)" (Gundling & Wildman, 2015, p. 5).

Perhaps the most famous example of plasticity in response to poor maternal nutrition concerns a population of pregnant women in the Netherlands during the Second World War. Between November 1944 and May 1945, these women experienced a famine precipitated by the

conditions of the war. Shorter gestation and correspondingly lower birthweights of neonates were experienced by women who suffered through the famine during the first two trimesters of pregnancy. However, shorter gestation and lower birthweights were not seen in women who experienced famine exclusively during the third trimester. This is in contrast to their own mothers, who also suffered through famine but experienced lower birthweights as a result of famine-exposure in the third trimester. Therefore, "clear effects on reproductive outcomes are seen in the generation following an environmental exposure in utero" (Lumey, 1992, p. 240). Another study used the children of the first-generation mothers. Based on evidence of decreased methylation, an epigenetic mechanism, of a gene associated with fetal growth, insulin growth-factor 2 (IGF2), the authors surmised that the placenta can plastically respond to environmental conditions such as low nutrition by limiting fetal growth (Heijmans et al., 2008).

Obstetric Disorders

In comparing different generations undergoing environmental stress, the above studies are means to explore not only placental plasticity and adaptiveness, but also the incidence of obstetric disorders. For example, the chronic hypoxia study has been employed as a way to understand the origins of disorders such as pre-eclampsia and intrauterine growth restriction (IUGR). Chronic hypoxia, which causes reduced uterine artery blood flow, can lead to IUGR, and in turn, small for gestational age newborns with low birthweights and high rates of mortality (Moore et al., 2004). The risks do not end after the early life period, as IUGR "may program the fetus for increased adult susceptibility to diabetes, obesity, and poor cardiovascular health (Barker, 1995; Barker, 1998; Eriksson et al., 2010; Godfrey & Barker, 2001; Kuzawa & Adair, 2004)" (Abrams & Rutherford, 2011, p. 423). Among the cardiovascular ailments are hypertension and coronary heart disease (Guo et al., 2008). These ailments may be a result of a mismatch between

fetal adaptations for low nutrition and enriched nutrition later in life (Gluckman, Hanson, & Buklijas, 2010).

While pregnancies at high altitudes are at particular risk for IUGR by way of the hypoxic environment, IUGR is common in other parts of the world, including the United States, in which 10% of pregnancies are affected (Diplas et al., 2009). The general cause of IUGR is uteroplacental insufficiency, which arises due to improper implantation and decreased placental invasiveness. This can be seen as a manifestation of the maternal-conflict, as the mother reduces the amount of nutrients transferred to the fetus to detrimental effect (Gundling & Wildman, 2015). In a study by Sitras, Paulssen, Leirvik, Vårtun, and Acharya, the authors conclude that "IUGR due to placental insufficiency appears to alter placental glucocorticoid metabolism, upregulates inflammatory response in placenta" (Sitras, Paulssen, Leirvik, Vårtun, & Acharya, 2009, p. 701). Placental glucocorticoid metabolism is associated with heightened maternal stress. In mice, genomic imprinting has been associated with IUGR in the form of deleted paternally expressed genes; however, "no primary epigenetic abnormality has been documented to cause human IUGR, although deregulation of several imprinted genes have been implicated previously (McMinn et al., 2006)" (Guo et al., 2008, p. 80).

As established, improper remodeling of the maternal vasculature can result in lower birthweights, putting newborns at greater risk of death. Moffett et al. describe how the combination of killer-cell immunoglobin-like receptors (KIRs) and paternal human leukocyte antigen-C ligands (HLA-C) "inhibits cytokine secretion" by the uterine natural killer cells (uNK), thereby decreasing birthweights. However, there is likewise a risk for newborns with high birthweights, which signifies dysfunctional fetal 'success' in the maternal-fetal conflict. High birthweights are

associated with excessive invasion of the placenta, and childbirth may be obstructed as a result (Moffett et al., 2015).

Obstetric disorders can be interrelated, such as with IUGR, which is pathogenically similar to severe preeclampsia (Sitras et al., 2009). More generally, both IUGR and pre-eclampsia are strongly correlated with a disintegration in maternal-fetal communication (Gundling & Wildman, 2015). According to Abrams and Rutherford, pre-eclampsia "is the primary cause of maternal mortality in resource-rich countries and the second leading cause…of maternal mortality and morbidity worldwide (Fisher, 2004; Hawfield & Freedman, 2009)" (Abrams & Rutherford, 2011, p. 6). Abrams and Rutherford describe pre-eclampsia as the "shallow trophoblast invasion and insufficient remodeling of maternal vessels (Fisher, 2004)" (Abrams & Rutherford, 2011, p. 6), a situation in which the mother is successful in the maternal-fetal conflict. In response to limited nutrition, the fetus damages maternal tissues in order to extract more nutrients. However, the mother cannot control this damage because as a result of the escalating maternal-fetal conflict, the fetus has evolved to "'ignore' most maternal advice as potentially self-interested" (Haig, 2015, p. 3).

Failures in maternal-fetal cooperation with respect to sub-optimal placental invasion are mirrored in postpartum hemorrhage (PPH), which surpasses pre-eclampsia in terms of maternal mortality rates worldwide. Instead of placental invasion being too shallow, the placenta can penetrate too deeply into the uterine wall. When an overly-invasive placenta detaches from the uterine wall following childbirth, the mother may experience catastrophic blood loss (Abrams & Rutherford, 2011). Due to excessive fetal control of the maternal vasculature, uterine muscle contraction to stop bleeding is compromised. Abrams and Rutherford argue that PPH represents "an evolutionary novel condition in hominins" due to "the particularly invasive nature of the

human placenta" (Abrams & Rutherford, 2011, p. 1). Abrams and Rutherford adopt an evolutionary approach by citing the transition to bipedalism and the subsequent transformations in pelvic anatomy as causes of "vascular remodeling to counteract gravitational effects (Rockwell et al., 2003; Abitbol, 1993)" (Abrams & Rutherford, 2011, p. 9). They further argue that "human vulnerability to PPH and other placental disorders related to trophoblast invasiveness arose around the same time as routinely bipedal locomotion" (Abrams & Rutherford, 2011, p. 10).

Another obstetric disorder related to severe trophoblastic invasion is placenta percreta, an extreme form of placenta accrete, "in which the placenta completely penetrates the myometrium, in some cases migrating out onto organs outside the reproductive tract, such as the rectum or kidneys (Moore & Gonzales, 2008)" (Abrams & Rutherford, 2011, p. 7). Additionally, highly invasive placentas can lead to "gestational trophoblastic diseases such as choriocarcinoma, a neoplasm that can metastasize to the lungs and cause death years after pregnancy (Shintaku et al. 2006; Smith et al. 2005)" (Abrams & Rutherford, 2011, p. 7). Moreover, there are considerable connections among placental invasiveness, genomic imprinting, and cancer. As the placental trophoblast has invaded deeper into the uterine wall as a result of the maternal-fetal conflict, it has bypassed maternal defense mechanisms, reminiscent of, and associated with, malignant cancer cells (Haig, 2015; Summers, Da Silva, & Farwell, 2002). Haig lists the common attributes of cancer and invasiveness as "rapid proliferation, invasion of neighboring tissues, deportation to distant sites, vasculogenic mimicry, induction of angiogenesis and modulation of immune responses" (Haig, 2015). According to Haig, "these adaptations can be co-opted by cancer" (Haig, 2015, p. 1). The expression of paternally derived genes may also be a culprit, as it may undermine attempts to control excess growth, as in the development of tumors (Summers et al., 2002). The

common thread among all of these obstetric disorders is the ongoing evolutionary conflict between mother and fetus for control over the nutrient supply.

Conclusion

Haig emphasizes the "inherent instability" of pregnancy, as the "classical distinction between physiology and pathology breaks down because what benefits one party may harm the other" (Haig, 2015, p. 3). Indeed, pregnancy represents a delicate balance between the interests of the mother, the father, and the fetus. When this balance is compromised, the consequences include a plethora of obstetric disorders. These obstetric disorders are not confined to gestation and childbirth, but ultimately portend long-term health implications for both the mother and the child. Understanding the underlying evolutionary mechanisms that have contributed to obstetric disorders is imperative to understanding those disorders themselves. As researchers continue to disentangle the many threads of maternal-fetal health vis-à-vis the placenta, evolving epidemiological and treatment efforts will ameliorate the health outcomes of women and children worldwide.

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